Host-microbe Interactions: Commensal Fungi in the Gut

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Abstract

Fungi are ubiquitous microbes that are common in diverse environments including as commensal organisms on the human body. In addition to its obvious role as a digestive organ, the intestines have been further appreciated as important for the development, maintenance, and instruction of the immune system. The gut harbors many types of microorganisms including bacteria, archaea, fungi, and viruses, and many studies over the past couple of decades have documented an important role for intestinal bacteria in immunological function. Recent studies are now suggesting that intestinal fungi (the gut "mycobiome") may similarly play important roles in host immunity and inflammation. This review will discuss recent studies that will influence our growing understanding of the role(s) of intestinal fungi in health and disease.

INTRODUCTION

Growing evidence documents that the mammalian gut is home to a diverse population of fungi that co-exist with other microbes in the intestinal microbiome including bacteria and viruses [1] (Fig. 1). Many of these fungi such as *Candida* spp. or *Saccharomyces cerevisiae* are well-known to most biologists, while most others such as *Wallemia* spp. or *Cladosporium* spp. are less well-known. Current definitions of the richness of the mammalian gut mycobiome mostly make use of culture-independent sequencing methods involving PCR amplification of internal transcribed spacer regions (ITS1 or ITS2) of fungal ribosomal DNA (rDNA) for species identification [2]. Characterizing fungal communities can be more challenging than bacterial communities due to uncertain methods of genomic DNA isolation, variations in the lengths of ITS regions in different fungi that influence PCR efficiencies, and insufficient reference databases. Further, we are still in early stages of understanding "normal" fungal diversity, time- and diet-based fluctuations, and the contributions of environmental exposures to definitions of the fungal microbiota [3]. Nevertheless, growing numbers of studies are suggesting that the intestinal mycobiome is

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skewed in the context of diseases including obesity, asthma, cirrhosis, and autism [4–6]. The potential for fungal dysbiosis to influence disease progression will be an active area of research in coming years.

INTESTINAL FUNGAL MICROBIOTA

The intestinal mycobiome

A good balance of microbial communities in the gut and immune responses to intestinal microbes is essential for mammalian health. In most studies cataloging fungi found in the intestines of humans or mice, over 50 genera of fungi are commonly reported, although 10 or fewer typically account for vast majority of organisms detected [3,7]. The fungi most commonly reported in the intestines of mice and humans include Saccharomycetes including *Candida* and *Saccharomyces* spp., Eurotiomycetes including *Aspergillus* and *Penicillium* spp., Tremellomycetes including *Cryptococcus* and *Trichosporon spp.* as well as *Cladosporium*, *Wallemia*, and *Malassezia* spp. [4,7–15]. Some reports also include robust detection of fungi such as *Phoma*, *Alternaria*, *Sclerotinia* and others which are primarily plant pathogens and are likely to be carried by food or other environmental sources.

Alterations in the intestinal microbiome are associated with many diseases, and alterations (dysbiosis) of fungal communities may contribute to disease susceptibility or disease severity. Many factors can likely promote fungal dysbiosis including exposure to antibiotics, diet, or genetic diversity. Exposure to antibacterial antibiotics has long been known to promote overgrowth of *Candida* in the gut [16]. Similarly, treatment of mice with antifungal antibiotics reduces the prevalence of some fungi, while it increases the prevalence of others [10]. The genetics of the host can influence the fungal microbiota. Mice deficient in CARD9 or Dectin-1 have been reported to have alterations in bacterial and fungal communities including changes in overall fungal burden as well as specific alteration in Microbotryomycetes and Lactobacilli [17–19], although how reproducible this is in the context of diverse facilities with diverse baseline microbiota is not yet clear. We are only beginning to understand the factors that promote colonization and growth of certain fungi in the gastrointestinal tract.

Requirements for allowing *Candida* colonization

Candida albicans is probably the most well-known intestinal fungus, being both a commensal in healthy individuals and an opportunistic pathogen of the gastrointestinal tract as well as of other mucosal surfaces (e.g. skin and vagina) and the blood. Studies on the mechanisms by which *Candida* colonizes the gut may provide insights into how fungi establish themselves in the intestinal environment. Treatment of people or mice with oral antibiotics can permit expansion of intestinal *Candida* populations, and in mice this has been established as a model for GI *Candida* overgrowth and long-term colonization [20].

A recent study demonstrated that the mice colonized with *Bacteroides thetaiotamicron* are more resistant to *C. albicans* colonization. The authors proposed that *B. thetaiotamicron* stimulates colonocytes to express hypoxia-inducible factor-1α (HIF-1α), leading to production of antimicrobial peptide LL-37 (CRAMP in mice). Elevated levels of CRAMP

contributed to killing of *Candida* and restricted GI colonization with the fungus [21] (Fig. 2). These findings suggest that inter-kingdom symbiosis between bacteria and fungi may be regulated, at least in part, by host immune responses to specific populations.

With respect to *Candida*, it is not clear what dictates the difference between commensal colonization and development of infectious disease. *Candida albicans* is a dimorphic fungus, meaning that it can grow in yeast and hyphal forms, and this ability to switch morphologies is linked to pathogenesis [22]. In addition, yeast can take on different morphologies including "opaque(a/α)" and "grey" as well as a morphology specifically associated with GI growth termed "gastrointestinally induced transition" (GUT) cells [23]. How these changes influence commensal colonization are still being worked out, but they likely reflect metabolic changes as well as changes in how the different types of cells interact with host tissues and immune cells. Until recently, *Candida* was not thought to produce lytic toxins targeting host cells, but a new study now reports that that the hyphal form of *C. albicans* secretes an amphiphilic cytolytic peptide, candidalysin, that disrupts epithelial cell membranes and promotes invasive disease [24].

INTESTINAL DISEASE

Inflammatory Bowel Disease

Crohn's disease (CD) and ulcerative colitis (UC) are the major clinical forms of inflammatory bowel disease (IBD), a chronic inflammatory disease of the gastrointestinal tract [25]. The causes of IBD remain elusive, although data suggest that variations in environmental factors, host genetics, and gut microbiota, all contribute to susceptibility to disease. As the mycobiome has gained attention for its role in promoting both health and disease, several studies have begun to investigate whether there is evidence of fungal dysbiosis or altered immune responses to fungi in IBD patients [9,14,15,26,27].

Dectin-1 (*CLEC7A)*, C-type lectin receptor, is a key innate immune receptor involved in coordinating host defense against fungi. It recognizes β-1,3-glucan, a major structural component of fungal cell walls [28]. Dectin-1 triggers phagocytosis of fungi and production of reactive oxygen species in macrophages and dendritic cells (DCs) and signals through CARD9 and NF-κB to direct production of inflammatory cytokines. Iliev *et al.* elucidated a central role of Dectin-1 in regulating the severity of colitis using the mouse DSS-induced colitis model [9]. Dectin-1 deficient mice were more susceptible to colitis, showing increased weight loss, pro-inflammatory cytokines, and delayed recovery from colitis (Fig. 2). Furthermore, they found that polymorphic variants in the *CLEC7A* gene are associated with increased severity of disease in ulcerative colitis patients, adding to previous studies showing a strong link between polymorphisms in *CARD9* and IBD [9,29].

Recently Sokol et al. observed a decrease in α-diversity (species richness) of the fungal microbiota and an increase in the fungi-to-bacteria diversity ratio in fecal samples from over 200 IBD patients (mixed CD and UC) relative to a handful of healthy controls [14]. Ascomycota and Basidiomycota were the major phyla present in the fungal communities of both healthy subjects and IBD patients, and the Basidiomycota/Ascomycota ratio appeared to be elevated in IBD patients compared to controls. Specifically, the prevalence of *Candida*

albicans was observed to be elevated in IBD patients, while *Saccharomyces cerevisiae* was reduced. Furthermore, correlation analysis revealed that the microbial network, including bacteria-fungi interactions, was altered in IBD patients compared to healthy subjects. The investigators noted stronger interactions between fungi and bacteria in UC patients whereas there was an uncoupling effect between the two in CD. These data suggest that fungi may differently influence how UC and CD develop.

Hoarau and coworkers take a slightly different approach in analyzing the micro- and mycobiome in IBD, specifically CD, by directly comparing CD patients and their healthy, non-CD relatives (NCDR) [15]. In this study, CD and NCDR samples did not differ in mycobiota diversity. Similar to Sokol et al., this study observed elevated *Candida* (although in this case *Candida tropicalis*) in CD patients. Anti-*Saccharomyces cerevisiae* antibodies (ASCA) are commonly found in the serum of IBD patients where these antibodies recognize mannan, a component in the fungal cell wall (including *Candida* spp.) [30]. Indeed, the authors observed elevated ASCA levels in the CD group, and they also noted a positive association between the presence of ASCA and *C. tropicalis* abundance in the CD group, suggesting immune responses to the intestinal fungi. In this group's analysis of bacteria-fungal interactions, they specifically noted a positive association between *C. tropicalis* and *Escherichia coli* and *Serratia marcescens*. *In vitro* experiments revealed that together these three species generate a thicker biofilm than any of the species generate alone, leading the investigators to hypothesize that the organisms may synergize to establish a commensal niche. Investigating whether this triple-species biofilm forms in the gut and affects immune responses may provide novel insight about the pathogenesis of CD.

Irritable bowel syndrome (IBS)

Irritable bowel syndrome (IBS) is a gastrointestinal disorder causing cramping, abdominal pain, bloating, gas, diarrhea and constipation that is influenced by diet, lifestyle and stress [31]. Unlike IBD, IBS is not associated with overt inflammation or damage to intestinal tissues. However, a subset of IBS patients experiences visceral hypersensitivity, which is a lowered threshold for pain in the abdominal area. Although alterations in bacterial communities in IBS have been investigated, the potential role for fungi in IBS remains largely unexplored [32]. A provocative recent study now sheds light on fungal dysbiosis in IBS patients and how changes in the mycobiome may mediate visceral hypersensitivity [33]. The fecal mycobiome was compared amongst IBS patients that were categorized into hypersensitive and normally sensitive groups. Analysis of these groups revealed that the hypersensitive IBS patients have a different mycobiota compared to the normally-sensitive IBS patients. Utilizing a rat model of stress-induced IBS-like visceral hypersensitivity, the authors observed that treatment with an antifungal drug, high doses of soluble β-glucan (thought to inhibit the fungal β-glucan receptor Dectin-1), or a pharmacological Syk inhibitor (also aimed at inhibiting Dectin-1 signaling) could block development of visceral hypersensitivity. Additionally, gavage of cecum content from hypersensitive rats was able to restore visceral hypersensitivity in fungicide-treated recipient rats. Visceral hypersensitivity has been previously linked to mast cell degranulation [34], and the authors documented that particulate β-glucans (which can activate Dectin-1), can trigger histamine release from gut mucosal mast cells (Fig. 2). If this mechanism truly contributes to IBS visceral

hypersensitivity, it will be important to understand how fungal antigens make their way from the gut lumen to mast cells in the mesentery and if activation of other antifungal immune receptors similarly affect development of visceral hypersensitivity.

Fungal influence on metabolites in the gut

Commensal fungi may directly or indirectly regulate gut homeostasis in many ways, and one recent hypothesis is that commensal fungi may influence the availability of specific biologically important metabolites [35]. *Saccharomyces*, commonly found in many foods, is a part of commensal fungi in the gut and is generally non-pathogenic in healthy individuals. However, even commensal fungi have detrimental effects if the relative burden is increased during fungal dysbiosis. Round and coworkers noted that intestinal *S. cerevisiae* could exacerbate colitis in mouse 2,4,6-trinitrobenzenesulfonic acid (TNBS) and DSS models, and they noted that monocolonization of germ-free mice with *S. cerevisiae* caused epithelial cells to produce increased levels of uric acid, promoting disruption of the intestinal barrier and increasing intestinal permeability [35] (Fig. 2). Uric acid was also produced during the *S. cerevisiae*-exacerbated disease in wild-type animals, and pharmacological inhibition of uric acid production ameliorated disease. Further, the investigators noted that uric acid and ASCA were positively correlated in human IBD patient sera. This and other fungal-influenced metabolite production may be good targets for clinical intervention in disease in the future.

ROLES FOR INTESTINAL FUNGI IN SITES BEYOND THE GUT

Influence of intestinal fungi on development of mucosal immunity

The gut microbiota regulates local and distal sites of the immune system [36]. It has a crucial role in developing secondary lymphoid organs during neonatal periods, and germ-free mice lacking microbes have immature lymph nodes and spleens [37]. Murine lymph nodes (LNs) undergo a maturation process that begins at birth and involves a shift in addressin expression from MAd-CAM1 to PNAd, allowing for recirculating lymphocytes to enter [38]. These changes in LN maturation are mediated in part by a subset of retinol dehydrogenase+ (RALDH) DCs [39]. Soon after birth, these RALDH+ DCs travel from the intestinal lamina propria to the peripheral and mesenteric lymph nodes (mLNs, pLNs) and promote LN maturation.

Shi and coworkers observed that RALDH+ DCs do not accumulate in the LNs of germ free (GF) mice, resulting in a lack of organized structure and cellularity within secondary lymphoid organs. Further, they observed a similar reduction of RALDH+ DCs in gut- and skin-draining LNs in wild-type mice treated with an anti-fungal cocktail but not in mice with an antibacterial treatment. Oral gavage with a mouse commensal fungal species, *Candida tropicalis*, was sufficient to enhance migration of gut RALDH+ DCs, to peripheral lymph nodes and promotes development of gut lymphoid tissues [40] (Fig. 2). This effect on RALDH+ DC migration and lymphoid tissue development was not efficiently promoted by two other fungi, *Trichosporon asahii* or *Saccharomyces cerevisiae*, suggesting that certain fungal species are specifically relevant in this context. We do not yet know if RALDH+ DCs must come in direct contact with commensal fungi to successfully migrate to the peripheral

LNs or if they must phagocytose and present the commensal fungi to T cells to promote this development.

Influence of fungal dysbiosis on inflammation and immunity at distal sites

Huffnagle and coworkers have noted that high-level GI colonization with *C. albicans* in antibiotic-treated mice can exacerbate pathology in allergic airway disease models [41], and Wheeler *at al.* recently reported that inducing alterations in the existing fungal microbiome with antifungal drugs can similarly alter the course of house dust mite (HDM)-induced allergic airway disease [10]. Perturbing fungal homeostasis by oral treatment with the antifungal drug fluconazole reduced the prevalence of some intestinal fungi but allowed for increased growth of specific fungi including *Aspergillus, Wallemia* and *Epicoccum*. Anti-fungal drug-induced fungal dysbiosis or oral exposure to *Aspergillus, Wallemia* and *Epicoccum* caused increases in allergy-related antibodies (IgE and HDM IgG1), Th2 cytokine producing T cells (IL-4, IL-5, IL-10) and infiltration of eosinophils into the lungs upon HDM immunization [10].

Fujimura and coworkers investigated the influence of microbiome dysbiosis during the neonatal period in humans on developing multi-sensitized atopy and ultimately asthma [42]. By separating the neonates based upon their microbiome diversity, the authors defined three subgroups of neonatal gut microbiota (NGM1, NGM2, NGM3) and reported that NGM3 had the highest risk of developing atopy (heightened immune responses to allergens) by age 2 and asthma by age 4. Disruptions in the bacterial communities of NGM3 included a reduction in *Bifidobacteria*, *Lactobacillus*, *Faecalibacterium* and *Akkermansia*, coinciding with earlier studies showing atopy associated gut microbiome dysbiosis [43]. Important for this discussion, notable fungal changes associated with NGM3 included a decrease in *Malassezia* and an increase in *Candida* and *Rhodotorula* proportions. The specific functional consequences of these fungal changes have yet to be determined.

Cirrhosis is permanent scarring of the liver due to inflammation triggered by various factors such as abusive alcohol consumption, hepatitis infection, or autoimmune reaction. A major complication of liver cirrhosis is spontaneous bacterial peritonitis following treatments with antibiotics. As noted above, an unintended effect of antibiotic treatment can be fungal overgrowth and dysbiosis, and patients with cirrhosis are more susceptible to fungal infections [44]. Several years ago, investigators noted that patients with cirrhosis showed elevated serum ASCA levels and that ASCA levels correlated with disease severity [45]. More recently, a patient survey about the interaction between fungal and bacterial communities in cirrhosis suggested that the Bacteroidetes/Ascomycota ratio can predict future hospitalizations; a low ratio was associated with low hospitalizations [6]. Together the data suggest that an altered immune interaction with intestinal fungi may influence disease. Experimental evidence for this idea has been provided by Yang et al., observing that chronic alcohol feeding to mice resulted in increased intestinal fungal burden and that *Candida* is specifically expanded in the intestines of alcoholic patients [46]. These investigators noted that serum β-glucan levels were increased in the animals, and that development of liver disease was prevented in animals lacking Dectin-1. Specifically, the investigators propose

that Kupffer cells, liver-resident macrophages that express Dectin-1, are activated by gut-derived β-glucan to secrete IL-1β which drives liver damage.

CONCLUSION

The roles of intestinal fungi in health and disease have been underappreciated compared to commensal bacteria in the gut, and we are just beginning to develop an appreciation for the impact of intestinal fungi on diverse pathologies. Intestinal fungi may influence microbiota (bacterial, fungal, and others) community structure in the gut, may alter production and consumption of key metabolites in the gut, and may interact with host immune cells to influence immune development and homeostasis. All of these may influence host health and the development of disease in the gut and at peripheral sites. Future studies will help develop mechanistic understandings of these roles for commensal intestinal fungi and may lead to the development of novel therapeutic approaches to preventing or treating diverse diseases.

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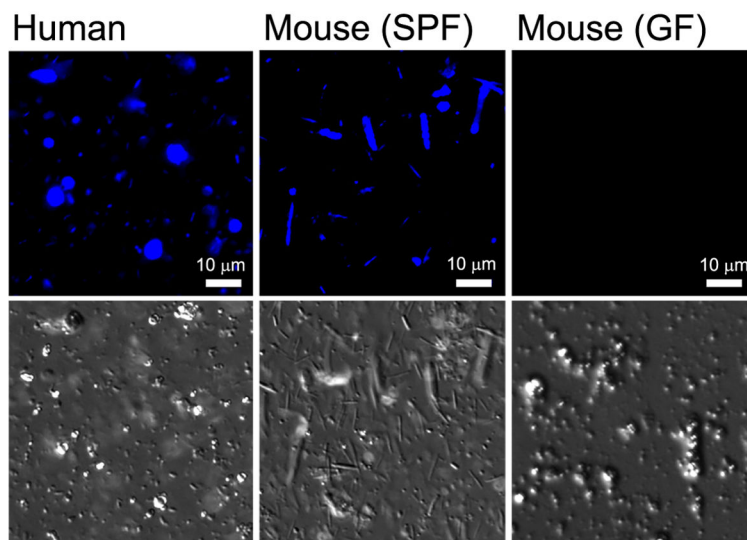
Highlights

- Fungi are commensal organisms in the mammalian gut.

- Fungal dysbiosis is associated with diverse diseases.

- Intestinal fungi shape development and maintenance of the immune system.

Figure 1. Fecal fungi

Fungi are easily detectable in stool samples from humans and specific pathogen-free (SPF) mice, but not in germ-free (GF) mice. Stool was collected and stained fresh with calcofluor white, a fluorescent dye that binds to chitin in fungal cell walls and is commonly used to detect pathogenic fungi in histology sections. Fungi are readily recognizable by their size and are distinct from plant material, which can also stain with calcofluor white but are not visible in the images shown.
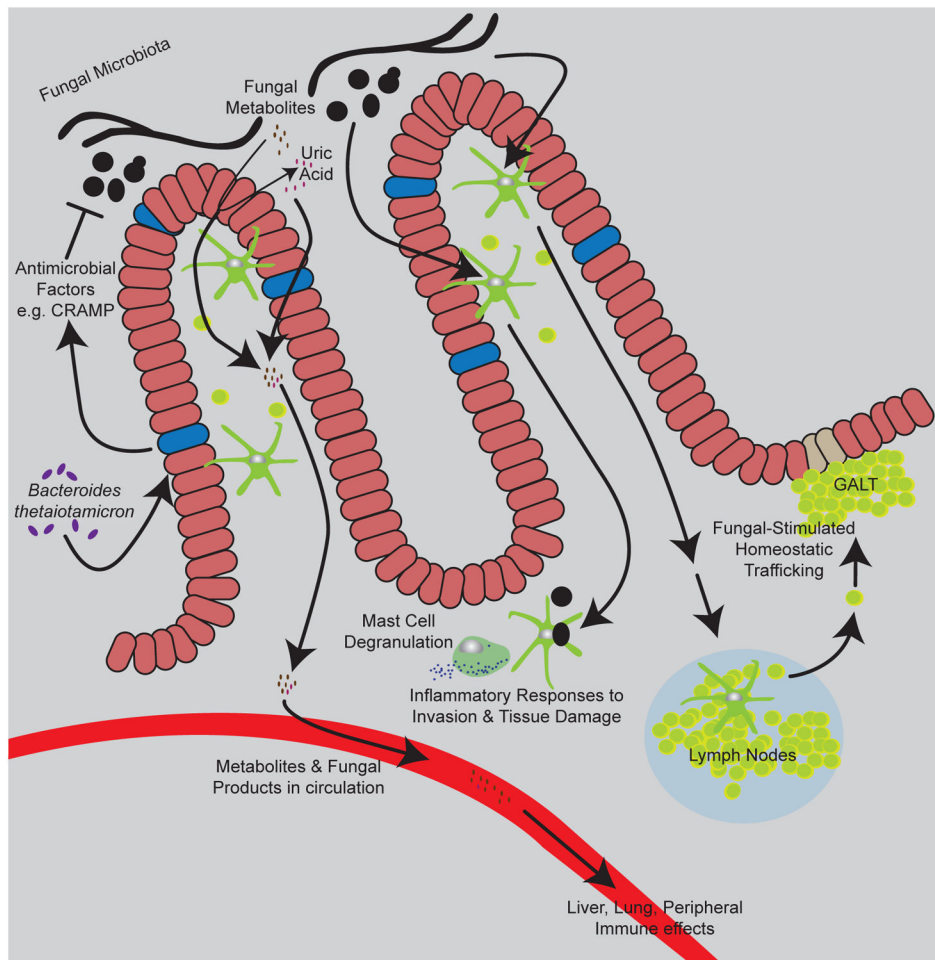
Figure 2. Diverse effects of commensal fungi

The diagram depicts many of the effects of commensal fungi discussed in the text. Bacterial microbiota and the intestinal epithelium influence the ability of fungi to colonize the gut. Commensal fungi produce metabolites and products that influence immunity and inflammation at local and distal sites. Immune cells in the gut respond to commensal fungi to influence inflammation and immune homeostasis.